Comprehensive Medical Management of Rosacea

An Interim Study Report and Literature Review

by [a]JAMES Q. DEL ROSSO, DO, FAOCD and [b]ERIC W. BAUM, MD

[a]Clinical Associate Professor (Dermatology), University of Nevada School of Medicine and Touro University College of Osteopathic Medicine; Dermatology Residency Director, Valley Hospital Medical Center and Las Vegas Skin and Cancer Clinics, Las Vegas and Henderson, Nevada; [b]Private Dermatology Practice, Gadsden, Alabama

ABSTRACT

Rosacea is a common inflammatory facial dermatosis seen in adults that exhibits considerable variety in clinical presentation. Multiple medical therapeutic options are available including topical and oral treatments. Optimal medical management of rosacea includes assessment of subtype and disease severity and use of appropriate skin care to reduce epidermal barrier dysfunction. This article provides an overall discussion of the medical management of rosacea and reviews interim results from a study evaluating the role of designated skin care in rosacea treatment.
(*J Clin Aesthetic Derm*. 2008;1(1):20–25.)

Rosacea is a chronic facial disorder characterized by varying degrees of erythema, telangiectasia, flushing, and the presence of inflammatory lesions, with intermittent periods of exacerbation and remission. Clinical symptoms and signs include stinging, burning, pruritus, scaling, and swelling (edema).[1,2] Although the condition is conventionally classified into several subtypes based on morphologic characteristics, these are not stages. There is no predictable progression from one subtype to another in any given patient. Differences in severity among patients within each subtype occur, and a patient may show clinical features of more than one subtype.[2]

The pathophysiology of rosacea is not fully understood, but it is believed to involve vascular and inflammatory components. It has been suggested that a proliferation of *Demodex* mites is involved in the pathogenesis of inflammatory lesions in selected cases, likely through an indirect mechanism due to triggering of inflammatory pathways. Dermal matrix degradation and chronic damage to superficial cutaneous vasculature are the sequelae of chronic photodamage (ultraviolet [UV] light exposure), via the production of reactive oxygen species and upregulation of protease enzymes that increase degradation of dermal collagen and elastic tissue.[2–4] Recent research has found high levels of cathelicidin and serine protease in the skin of patients with rosacea as compared to normal skin of subjects without rosacea, suggesting the contribution of these two factors to the inflammatory component of rosacea.[5] Genetic predisposition and various environmental triggers also appear to play a role in the disorder. Identified environmental triggers are numerous and dependent on the susceptibility of individual patients. The more commonly reported triggers include sunlight, heat, cold, wind, consumption of spicy food or alcohol, and stress.

Epidermal barrier dysfunction, characterized by increased transepidermal water loss (TEWL) predominantly involving the central facial region, seems to play an important role in both inflammatory (papulopustular) and erythematotelangiectatic rosacea, which partially explains the clinical observation of "sensitive facial skin" in rosacea.[6,7] The symptoms and signs commonly expressed by the patient are the same as those that have been formally captured at baseline in rosacea studies before initiation of treatment, suggesting that they are an integral component of the disease itself. Such symptoms and signs include stinging, burning, pruritus, facial discomfort, dryness, and scaling.[6-8] External irritants, which may be included in many poorly selected skin-care and cosmetic products, can exacerbate signs and symptoms of rosacea.[2,6]

The complex, multifactorial pathophysiology of

DISCLOSURE: Dr. Del Rosso is a cosultant to, speaker for, and performs research for Allergan, Amgen, Coria, Galderma, Intendis, Medicis, OMP, Ortho Neutrogena, QLT, Ranbaxy, SkinMedica, Stiefel, Triax, Unilever, and Warner Chilcott. Dr. Baum has no conflicts of interest.
ADDRESS CORRESPONDENCE TO: James Q. Del Rosso, DO, FAOCD; e-mail: jqdelrosso@yahoo.com

rosacea supports the need for an appropriately designed management program. With regard to medical management, a three-pronged approach, incorporating patient education, proper skin-care recommendations, and appropriate medication selection, is more likely to lead to therapeutic success. Medical treatment strategies, though not curative, can effectively reduce inflammatory lesions and facial redness, especially perilesional erythema. Appropriate skin-care management can help repair and maintain skin-barrier integrity, reduce symptoms and signs of the disease, and augment the therapeutic benefit of medications. Patient education is vital to help provide a better understanding of the disease state itself and to set realistic patient expectations regarding therapy in terms of the magnitude of improvement and the time course of response. According to the National Ambulatory Medical Care Survey, patients receive limited face-to-face contact time with the dermatologist during office visits.[9] Importantly, dermatologists will be most time efficient and more successful if their clinical staff are involved in educating patients regarding the details of the management program. An initial investment in thorough instruction on the disease state, treatment options, adherence to prescribed therapy, selection of skin-care products, details on use of the skin-care regimen, avoidance of excessive exposure to sunlight and other known triggers, and how and when to use their medications will likely save time later and make office visits more efficient and productive, resulting in better outcomes.

TREATMENT STRATEGIES

Current medical treatment strategies for rosacea aim to reduce the number and severity of inflammatory lesions and decrease erythema and include both topical and systemic agents.[10]

Topical agents. The choice of topical agents for use in rosacea is based on various criteria, including mechanism of action, efficacy and tolerability, patient skin type, and response to previous therapy.[2,10] Several topical therapeutic options for the treatment of rosacea appear in the literature and have been discussed elsewhere. This article will focus on the major topical agents that have an indication for rosacea based on approved labeling.[1,10,12] The three topical therapies with indication from the Food and Drug Administration (FDA) for rosacea are sulfacetamide 10%/sulfur 5% (sulfacetamide/sulfur), metronidazole, and azelaic acid (AzA) 15% gel.[10,12]

Other topical agents, such as the topical antibiotics (clindamycin, erythromycin), calcineurin inhibitors (tacrolimus, pimecrolimus), and benzoyl peroxide-clindamycin, are sometimes employed as second-line agents, although there is limited data to support their use.[10,12]

Oral agents. Anti-inflammatory–dose doxycycline (40-mg delayed-release capsule formulation administered once daily) is the only oral agent approved

First-line Topical Treatments for Rosacea

Sulfacetamide/sulfur was introduced in 1956 and is available commercially as a gel, cleanser, lotion, topical suspension, and cream (with and without sunscreen).[2,10] Although the mechanism of action of sulfacetamide/sulfur is not clear, an anti-inflammatory effect is believed to play a role. Indications for use of sulfacetamide/sulfur are rosacea, acne vulgaris, and seborrheic dermatitis. Sulfacetamide/sulfur reduces inflammatory lesions and perilesional erythema of papulopustular rosacea, may contribute to reduction in background erythema, and assists in reduction of associated facial seborrheic dermatitis in patients with "rosacea-seborrheic dermatitis overlap."[2,10]

Topical metronidazole was introduced in 1989, first as a 0.75% gel, and later as a 0.75% lotion and cream, and a 1% cream and gel.[2,10] The mechanism of action of topical metronidazole for rosacea is believed to relate at least partially to anti-inflammatory activity, mediated through reduced release of reactive oxygen species from neutrophils. Topical metronidazole is the first agent approved by the FDA specifically for the treatment of rosacea. Metronidazole reduces inflammatory lesions and perilesional erythema of papulopustular rosacea and may contribute to reduction in background erythema.[2,10]

AzA 15% was introduced in 2002 as an aqueous-based gel formulation that has been shown not to disrupt the epidermal barrier, and is the most recent FDA-approved topical therapy for rosacea.[2,10,13,14]

The mechanism of action of AzA in rosacea is believed to be anti-inflammatory and antioxidant, with reduction in reactive oxygen species released from neutrophils. Although the 15% gel formulation has a 5 percent lower concentration of AzA than the AzA 20% cream vehicle (approved for acne vulgaris), the 15% gel formulation provides better percutaneous drug delivery than the 20% cream.[12] AzA reduces inflammatory lesions and perilesional erythema of papulopustular rosacea and may contribute to reduction in background erythema.[2,10,15,16]

by the FDA for treatment of rosacea. It is proven in rosacea to be as effective as doxycycline 100mg daily, with a similar onset of therapeutic action and significantly fewer adverse events, especially gastrointestinal (GI) side effects.[11,12] Additionally, unlike oral antibiotic doses of tetracycline agents, such as tetracycline, minocycline, and doxycycline (50mg daily or higher), anti-inflammatory–dose doxycycline is devoid of antibiotic activity, even when used on a chronic basis.[11,12] For this reason, anti-inflammatory–dose doxycycline (administered once daily as indicated in approved labeling) is not categorized by the FDA as an antibiotic, as it exhibits only anti-inflammatory activity. A number of oral antibiotics have been used off-label for rosacea based on widespread clinical experience, a small collection of studies, and case reports. At conventional doses (antibiotic doses), oral antibiotics produce selection pressure and have been shown with both short-term and long-term use to be associated with emergence of bacterial strains less sensitive to antibiotics. This latter point has been demonstrated recently with both doxycycline 100mg daily and with standard doses of azithromycin.[12] The effectiveness of anti-inflammatory–dose doxycycline or oral antibiotics in reducing signs and symptoms of rosacea is believed to be related to their anti-inflammatory properties.[2]

SKIN-CARE MANAGEMENT

Patients with rosacea have sensitive skin that flushes easily. Burning, stinging, and itching are common, which are partially due to disrupted skin-barrier function, characteristically seen in patients with rosacea.[6–8] The stratum corneum is composed of corneocytes, which are held together by desmosomes and an intercellular lipid membrane comprising physiologic lipids that serve to regulate TEWL. Proper skin care can help repair and maintain the intercellular lipid membrane of the epidermal barrier.

As an integral component of the overall management of rosacea, the suggested skin-care regimen utilizes products containing synthetic detergent surfactants and optimized occlusive and humectant moisturizing components to minimize the effects of skin-barrier dysfunction and reduce skin irritation.[6,10,17,19] In addition, it is recommended that rosacea patients routinely use a high SPF (≥15) product to avoid UV-light-induced dermal destruction attributed at least, in part, to reactive oxygen species and upregulation of enzymes, which degrade the dermal matrix.[7,10,18–20] Some patients may also wish to use cosmetic camouflage to conceal erythema and telangiectasias.

SELECTION OF SKIN CLEANSERS

Soap-based cleansers are not considered appropriate for patients with rosacea as they are alkaline and produce more damage to the skin barrier.[7,21,22] Synthetic detergents (syndets) are less irritating and drying and have a pH more compatible with natural skin acidity. Foaming face washes and lipid-free cleansers are also appropriate.[7,18,22–24]

SELECTION OF MOISTURIZERS

Moisturizer use is suggested for patients with rosacea who should incorporate humectant and occlusive agents that have the potential to replenish depleted lipids within the impaired epidermal barrier and to restore its ability to retain moisture.[25,26] Humectants (e.g., glycerin) attract and hold moisture within the epidermis, increasing hydration and allowing for enhanced penetration of topical pharmacologic agents. Occlusives (e.g., petrolatum, silicates) minimize desiccation by preventing evaporative and TEWL. The beneficial effect of suitable moisturizers on skin-barrier function may result in perceptible improvement in symptom relief among patients with rosacea (see below).[18,25,27]

FROM THEORY TO PRACTICE: THE ASC STUDY

The Assessment of Skin Characteristics (ASC) study* is an ongoing, open-label, multicenter study in which patients with mild-to-moderate inflammatory (papulopustular) rosacea are instructed to use a defined skin-care regimen that is recommended professionally during their dermatology office visits. The program includes a designated facial cleanser and moisturizer used in conjunction with a provided topical medication. The aim of the study is to assess the effect of the entire regimen, as well as the specific impact of the moisturizer component, on relief of symptoms and signs of rosacea.

STUDY DESIGN

The study uses a split-face design. At baseline, prior to initiation of treatment, symptoms (stinging, burning, tingling, pruritus) and signs (inflammatory lesions, erythema) of rosacea are recorded, along with designation of severity. After washing the entire face with the provided cleanser, patients are instructed to apply AzA 15% gel to both sides of the face, with the subsequent application of the provided moisturizer on one designated side of the face only. Patients then record scores for occurrence and severity of stinging, burning, tingling, and itching on each side of the face.

This article provides an interim report inclusive of results from the first 24 enrolled and completed subjects from multiple investigators in different practice locations across the United States.

INCLUSION CRITERIA

The inclusion criteria include patients 18 years of age or older with mild-to-moderate inflammatory (papulopustular) rosacea.

EXCLUSION CRITERIA

Exclusion criteria include treatment with topical agents in the preceding two weeks, oral agents (antibiotics, anti-inflammatory–dose doxycycline) in the preceding four weeks, or isotretinoin in the preceding six

months; pregnancy; breastfeeding; and concomitant skin or underlying medical conditions or treatments which the investigator determines may interfere with study results.

METHODS

Investigators enrolling patients are required to record baseline scoring on erythema and inflammatory lesions. Baseline skin characteristics and symptoms are also recorded, along with the skin-care regimen to be used. Patients are provided with AzA 15% gel, a designated facial cleanser (CeraVe™ Cleanser, Coria Laboratories, Ltd., Fort Worth, Texas, or Cetaphil® Gentle Cleanser, Galderma Laboratories, Fort Worth, Texas), and a designated facial moisturizer (CeraVe™ Cream or Cetaphil® Cream), and are instructed to adhere to the following procedure twice a day (in the morning and evening) for seven days:

1. Wash the face gently with the provided skin cleanser only
2. After gently drying the face, evenly apply AzA 15% gel to the entire face
3. Apply the provided moisturizer to the right side of the face only
4. Score sensations of stinging, burning, tingling, and itching on left and right sides of the face for severity (0=none, 1=mild, 2=moderate, 3=extreme) and duration in a patient diary in the morning and evening.

RESULTS

Patient characteristics and baseline clinical signs and symptoms are shown in Tables 1 and 2. All 24 patients completed the study, two patient diary scores were not available for any of the study days, allowing for reporting of endpoint data on 22 patients. An additional patient diary had no scores for the morning of Day 1. Mean scores for stinging, burning, tingling, and itching recorded for each side of the face in the morning and evening of the seven study days are shown in Figure 1.

Reported occurrence/severity of stinging and burning showed a downward trend over the seven-day period for AzA 15% gel both with and without the moisturizer. This is consistent with previous studies that show a decrease over time in reported stinging and burning in patients using AzA.[16] Although similar scores were recorded for all symptoms both with and without moisturizer use, all 14 data points for stinging with the moisturizer were below the corresponding data points for AzA without the moisturizer, and for burning, all but one were below and none were above. For tingling and itching, the differences were not marked, though after Day 3, all data points for AzA plus moisturizer, with the exception of one for each symptom, were below the corresponding data points for AzA without moisturizer use, and none were above.

DISCUSSION OF INTERIM REPORT RESULTS

The significance of this data from a preliminary subset of patients (n=22) must await clarification by results from the larger study. At this point, it may be tentatively concluded that (1) a regimen consisting of AzA 15% gel applied twice

Table 1.
Patient Demographics (N=24)

Females	18 (75%)
Mean age	46 (75%)
Race	
Caucasian	21 (87%)
Asian	3 (13%)
Skin type	
Normal	8 (33%)
Oily	9 (38%)
Dry	6 (25%)
Other	1 (4%)

Table 2.
Baseline Clinical Signs and Symptoms

Erythema	
Light red or pink	8 (33%)
Red	14 (58%)
Beet red	2 (8%)
Lesions	
1 to 10	15 (63%)
11 to 20	7 (29%)
>20	2 (8%)
Stinging	
None	7 (29%)
Mild	10 (42%)
Moderate	6 (25%)
Severe	1 (4%)
Burning	
None	8 (33%)
Mild	8 (33%)
Moderate	7 (29%)
Severe	1 (4%)
Tingling	
None	11 (45%)
Mild	9 (38%)
Moderate	3 (13%)
Severe	1 (4%)
Itching	
None	7 (29%)
Mild	12 (50%)
Moderate	3 (13%)
Severe	2 (8%)

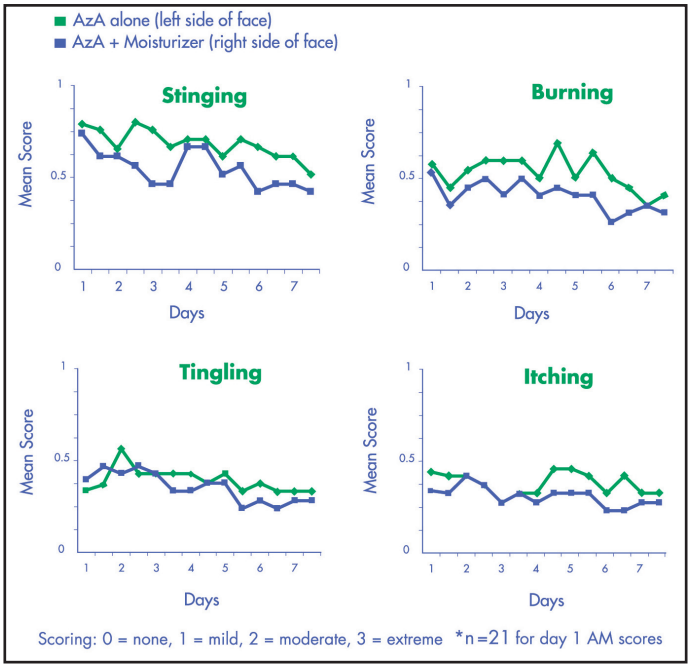

Figure 1. Mean scores (*n*=22) for stinging, burning, tingling, and itching, recorded over seven study days in the morning and evening.

daily after use of a dermatologist-chosen facial cleanser seems to mitigate symptoms of stinging and burning over time, and that (2) the concomitant use of a moisturizer may offer some added improvement in symptom relief. This would tend to support the comprehensive approach to rosacea management advocated here.

USE OF PHOTOPROTECTANTS

Long-term photodamage is thought to be a pathogenetic factor in rosacea.[19] In a survey of more than 1,000 patients with rosacea, 81 percent identified exposure to sunlight as a trigger for flare-ups, but only 5 percent reported the consistent use of a sunscreen.[28] Although ambient heat associated with sunlight exposure is likely to be a major contributing cause of an acute rosacea flare, photoprotection reduces dermal matrix degradation which contributes to progressive development of persistent erythema and telangiectasia formation, both cardinal features of rosacea. It is recommended that rosacea patients consistently use a photoprotectant (≥SPF 15) to avoid the dermal matrix degradation attributed at least, in part, to UV exposure; recommended photoprotectants are those with broad-spectrum formulations capable of filtering both UVA and UVB wavelengths.[7,10,18,20]

COSMETIC SELECTION

When selecting cosmetic and skin-care products, patients with rosacea are advised to avoid potential irritants.[7,20,23,29] Patient surveys have identified the following ingredients as most likely to cause a flare-up: alcohol, witch hazel, fragrance, menthol, peppermint, and eucalyptus oil.[23,30,31]

PATIENT EDUCATION

Managing expectations of rosacea patients through disease-state awareness completes the treatment triad and is vital to establish realistic outcomes and to promote treatment adherence. Patients need to be educated regarding the chronic and recurrent nature of rosacea. When goals for initial improvement and long-term maintenance are set with the patient, a partnership between the patient and the dermatologist and his/her staff is established. Key points on which patients will likely need to be counseled include:

Compliance with topical therapy. Patients need to understand the potential value of continuing topical therapy after signs and symptoms of the acute rosacea flare have resolved in order to maintain remission and prevent recurrence.[32] It has been reported that after discontinuing therapy, one-fourth of patients relapse after one month and two-thirds relapse after six months.[33]

Avoiding UV exposure. Time outdoors during maximum sunlight hours should be limited. A moisturizing sunblock should be used when outdoors during daylight hours.

Avoiding other known triggers. If patients are unsure of their own flare factors, they are encouraged to keep notes or a diary in order to identify their own individual triggers and then do their best to avoid them.

Using skin-care products and cosmetics recommended by their dermatologist/professional staff. Avoidance of soap-based facial cleansers is suggested. Cleansers containing synthetic detergents as well as foaming face washes and lipid-free cleansers are recommended.[7,18,21–24] Regular use of a moisturizer is also suggested to assist in reducing epidermal barrier dysfunction that has been observed in association with rosacea.[6,7,10,18,,25–27]

Using proper skin-cleansing technique. Patients should be taught to avoid vigorous scrubbing of the face. Washing should be done gently, with only the fingertips. Lukewarm water should be used—hot or cold water may trigger a flare of erythema and flushing.

CONCLUSION

Despite the availability of multiple medical therapeutic options for the treatment of rosacea, management of this disorder remains challenging. A combination of thorough patient education inclusive of reasonable outcome expectations, information on proper skin care, and use of available medical therapies is likely to optimize therapeutic success. The interim study results reported here support the importance of appropriate skin care in reducing symptoms and signs of rosacea, which may be a component of the underlying disease or a tolerability response to topical therapy, especially within the first week of treatment.

The limited time available to counsel patients during a busy day at a dermatology practice can make proper patient education about rosacea a challenge. Nevertheless, patients want and appreciate thorough

counseling about the disease they have and its management. The dermatologist may choose to delegate patient education to a staff member who is fully trained on what to discuss with the patient, as described above. It may also be helpful to supplement verbal education with handout materials (i.e., educational pamphlets from the National Rosacea Society, American Academy of Dermatology, non-branded materials provided by pharmaceutical companies) and credible online sources of information for patients such as www.rosacea.org. Once patients become more fully educated about rosacea, they can better work in partnership with their dermatologist to optimally manage this troublesome and chronic condition.

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*AUTHOR'S NOTE

Special thanks to the ASC study investigators: Eric Baum, MD; Michelle Barton, NP; and Steve Hawkes, PA-C. The ASC Study is an investigator-initiated study supported by a grant from Intendis.